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**Title:**

Long-term Health Related Quality of Life following Esophagectomy: A non-randomized comparison of Thoracoscopically-Assisted and Open surgery.

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[Prof](#) .Andrew Barbour and Dr. Orla Mc Cormack contributed equally to the manuscript.

**Running head:**

Quality of Life after Thoracoscopically-assisted Esophagectomy

**INTRODUCTION:**

Minimally invasive esophagectomy (MIE) is a surgical technique aimed at reducing the morbidity of esophagectomy while maintaining oncological adequacy and long-term survival.<sup>1</sup> An exploratory randomized trial comparing MIE with open transthoracic esophagectomy has shown improved short term outcomes and no compromise to the quality of surgical resection.<sup>2</sup> This trial was small, however, and not powered to examine survival or patient-centered outcomes. We have previously reported our experience with thoracoscopically-assisted McKeown esophagectomy (TAMK), demonstrating that it can be performed safely, with equivalent survival and patterns of recurrence when compared with open resection.<sup>3,4</sup> We have also reported on long term quality of life assessment in a small number of these patients.<sup>4</sup> Where clinical results and survival data are equivocal patient reported outcomes can offer insight into what might be the optimal approach. Health-related quality of life (HRQL) is an important outcome measure in surgical oncology as it covers a broader aspect of health.<sup>5</sup> The patients themselves complete the questionnaires so this data is relevant to the everyday life of the patient. Prospective studies assessing the impact of esophagectomy on HRQL consistently report that patients experience a general decrease in performance and severe fatigue lasting at least six months after surgery,<sup>5,6</sup> and some symptoms will persist in long-term survivors.<sup>4,7</sup> To date, five direct comparison studies between MIE and open esophagectomy with HRQL as a primary endpoint have been performed.<sup>8-12</sup> However, these are small studies with the longest follow up being 12 months post operatively. Long-term outcome data and information about long-term HRQL outcomes post minimally invasive esophagectomy are lacking. The present study was undertaken to examine and

compare self-reported HRQL scores for patients undergoing TAMK (with an open abdominal approach) with open transthoracic esophagectomy (Ivor Lewis operation) TTIL for esophageal or GEJ cancer using a validated HRQL instrument.

## **METHODS:**

### ***Health-related quality of life assessment***

Patients who consented to participate in HRQL analysis and who were able to speak and read English completed HRQL questionnaires before surgery (baseline, within 4 weeks of surgery), at 3 monthly intervals for the first 12 months following surgery, 6 monthly intervals to 24 months and annually thereafter to 5 years or until death or patient withdrawal from the study. The baseline data were collected within clinics in the hospital and subsequent questionnaires were mailed to patients unless additional help was required. Questionnaires were completed by the patients. If patients did not respond to questionnaires within 4 weeks another questionnaire was sent and an attempt was made to contact the patient by telephone from a research nurse. Questionnaires were checked for missing answers and if answers were absent, patients were contacted and asked to respond to the unanswered questions. HRQL items that remained unanswered were handled using imputation as recommended by the developers.<sup>13</sup> Patients with missing forms were excluded from analysis of the absent assessment points.

The instrument used was the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 (version 3.0) and Oesophageal Cancer Module QLQ-OES18.<sup>13-17</sup> The EORTC QLQ-C30 contains scales and items addressing functional aspects of HRQL and symptoms that commonly occur in cancer, as well as items assessing the financial impact of malignant disease and

global HRQL. The QLQ-OES18 module focuses on symptoms specific to oesophageal cancer treated with single or multimodal treatment. Both questionnaires have been validated.<sup>14</sup> All QLQ-C30 and QLQ-OES18 responses were linearly transformed to scores from 0 to 100.<sup>16</sup> For functional and global health status scales, a higher score represents a high/healthy level of functioning, whereas for a symptom scale or single item, a high score represents a high level of symptom/problem.<sup>16</sup> Mean scores were calculated at baseline and at each assessment point to 24 months for both groups of patients.

We collected information in a prospectively maintained esophagogastric cancer database. We identified 487 consecutive patients with esophageal or GEJ cancer selected for TAMK (with thoracoscopic mobilization) or TTIL (with an open thoracotomy) who had completed pre-treatment (baseline) HRQL questionnaires (Fig. 1) at the Princess Alexandra Hospital between 1998 and 2011. Permission to collect and use the information in the database was approved by the hospital ethics committee.

Tumour staging and Siewert classification was performed with endoscopy, computerized tomography of chest and abdomen and staging laparoscopy. Positron emission tomography (PET) scans were routinely performed from 2004. Endoscopic ultrasound, as it became available was used selectively for staging. Treatment decisions were all made at an upper gastrointestinal multi-disciplinary team meeting with surgery alone used as a result of randomization within clinical trials,<sup>18</sup> inability to receive neoadjuvant treatment or patient preference.

### ***Surgery***

All operations were performed with curative intent. The operative techniques have been described in detail previously.<sup>1, 3, 4</sup> TTIL was defined as resection of the

proximal stomach and thoracic esophagus via laparotomy for gastric mobilisation and right transthoracic esophagectomy with esophagogastric anastomosis in the chest (Ivor Lewis operation).<sup>19</sup> TAMK was thoracoscopically-assisted mobilization of the thoracic esophagus with a laparotomy approach to allow resection of the proximal stomach and construction of the gastric tube for an esophagogastric anastomosis in the neck.<sup>1</sup> The selection criteria for TTIL or TAMK were solely related to the site of the cancer and the degree of gastric resection required to achieve appropriate resection margins which would allow (or not allow) a gastric tube reconstruction to be taken to the neck for anastomosis. If there was more than 2cm of gastric cardia involved the Ivor Lewis approach (TTIL) was performed via thoracotomy solely to facilitate the anastomosis. Procedure-related mortality was defined as death in hospital and/or death within 90 days of operation.

### ***Follow-up***

Patients were followed clinically every 3 months for the first two years, six monthly for two years and annually to 10 years. Patients underwent cross sectional imaging and endoscopy when symptoms or signs were suspicious for recurrent disease.

### ***Data Analyses***

Statistical analysis was carried out with SPSS for Windows, version 17.0 (Statistical Package for the Social Sciences, SPSS, Inc., Chicago, IL), SAS, version for Windows 9.1 (SAS Institute, Cary, NC) and R (version 3.2.3). Continuous variables were expressed as median (minimum-maximum) and compared using the Mann Whitney test, whereas categorical variables were compared using the  $\chi^2$  or Fisher's exact test. Unadjusted differences in survival for categorical or continuous clinicopathological variables were compared via the Log Rank test or



Cox regression analyses, respectively. Overall survival probabilities were estimated by the Kaplan-Meier method, with differences in survival rates assessed using the log-rank test to determine univariable significance. Multivariable analysis was performed using forward stepwise Cox regression (entry criterion Wald) test, including post-operative AJCC stage, age, histological subtype, comorbidity and type of operation.

The difference from baseline was calculated for each HRQL parameter. A difference of  $\geq 5$  points was considered a significant change in HRQL, as has been previously reported.<sup>11, 20, 21, 22</sup> To allow for correlation of outcomes within individuals, generalised estimating equations (GEE) were employed.<sup>23,24</sup> Differences over time in mean HRQL scores between TAMK and TTIL adjusted for covariates selected *a priori* as potential modifiers of HRQoL including gender, age, histopathology, stage, neoadjuvant treatment and type of surgery were estimated and tested using GEE.

Additionally, in a separate analysis, GEE were employed with propensity score adjustment.<sup>25,26</sup> Propensity scores were calculated using the gbm package (version 2.1.1)<sup>27</sup> in R (version 3.2.3)<sup>28</sup>. The propensity scores were estimated by boosted regression of treatment (TAMK versus TTIL) on age, gender, histological type, neoadjuvant therapy, tumor site, clinical stage, American Society of Anesthesiologists (ASA) classification, and the presence of comorbidity (yes/no). Boosted regression was used to account for possible interactions between the included covariates. The distribution of boosted regression propensity scores between the TAMK and TTIL groups are shown in Supplementary Figure 1. They were then applied using the third method of Kurth et al (2006)<sup>29</sup> where GEE were adjusted using the propensity scores as a linear term. Following the recommendations of

Kurth et al, the inverse weighting methods were not employed since the weights of several individuals were very large. Note that, as expected, when adjusted for propensity scores, the pre-treatment covariates were not significantly different between surgery groups. In addition to the propensity scores, the GEE also included type of surgery and post-operative pathological stage, which were chosen *a priori* as potential modifiers of HRQoL. Results of GEE using boosted propensity score analysis are presented here since in most cases they were nearly identical to the results obtained from GEE adjusted for covariates (including gender, age, histopathology, stage, neoadjuvant treatment and type of surgery).

In addition, propensity scores were computed by logistic regression using the nonrandom package (version 1.42) <sup>30</sup> (data not shown). Analogous to our boosted regression model, treatment (TAMK versus TTIL) was regressed on age, gender, histological type, neoadjuvant therapy, tumor site, clinical stage, American Society of Anesthesiologists (ASA) classification, and the presence of comorbidity (yes/no). Adjustment of GEEs with propensity scores computed by boosted regression and logistic regression yielded highly similar results (data not shown).

Unless otherwise stated, a significance level of 0.05 was used for all statistical tests.

## **RESULTS:**

### ***Clinicopathological variables and survival***

Of the 487 patients, 377 underwent TAMK and 110 underwent TTIL (Table 1). The majority of the patients were male in both treatment groups. Age, ASA grade, and exposure to preoperative treatment were similar between groups. Average tumor length and R0 resection status were also similar between groups, but patients undergoing TTIL were significantly more likely to have an adenocarcinoma, tumor

involving the GEJ, and a more advanced tumor stage at resection (Table 1). Length of hospital stay was shorter in the TAMK group 13 days (8-123) compared to 15 days (8-56) in the TTIL group (Mann-Whitney,  $p < 0.01$ ). Due to the long period of the study, we analysed the patterns of care by 5-year time periods: 1998-2002; 2002-2007; and 2007-2011 (Supplementary table 1). Over the time period of the study, the only significant difference in treatment-related variable was an increase in the use of neoadjuvant therapy over time ( $p < 0.001$ ).

The median overall survival was 53 months (range 2-151) for TAMK compared with 24 months (range 5-135) for the TTIL group (Log rank,  $p < 0.01$ , Supplementary Figure 2). However, operative approach was not associated with overall survival in a multivariable model adjusting for [post-operative](#) AJCC stage, age, histological subtype, [comorbidity](#) and type of operation (Supplementary Table 2).

### ***Questionnaire compliance and missing data***

At the end of 2 years there were 60 patients (12%) with missing HRQL data and 153 patients (35%) had died. Attrition rates due to disease progression were high for both groups with 271 (72%) TAMK patients and 63 (57%) TTIL patients alive at 2 years (Table 2). Compliance during follow-up was generally very high with >99% at 3 and 6 months, >95% at 12 months and >85% at 24 months, Table 2. Clinical and sociodemographic data were similar in patients with and without baseline HRQL data and there were no differences in the completion rates between the two treatment groups.

### ***Health-related quality of life functional outcomes***

Patients selected for TAMK or TTIL reported similar baseline HRQL scores for all functional scales (Table 3 and 4, Student's t-test). Physical, role, and social

function deteriorated by over 15 points after TAMK and TTIL (Table 3). Mean physical and social function scores “recovered” to within 10 points of baseline at 12 months for the TAMK group but not the TTIL group (Supplementary Fig. 3). Mean role function scores “recovered” to within 10 points of baseline at 24 months for the TAMK group but did not for the TTIL group. Emotional function was low in both groups at baseline, decreased further at 3 months, but then steadily improved after surgery in both groups to overall higher scores at 12 months than at baseline (Supplementary Fig. 4). Similarly global quality of life scores were low at baseline, decreased at 3 months but thereafter improved with higher overall scores at 24 months in [both groups](#) (Supplementary Fig. 5).

Longitudinal analyses were undertaken comparing TAMK and TTIL using GEE with propensity score [adjustment \(propensity scores are shown in Supplementary Figure 1\)](#). There were no significant differences between the TAMK and TTIL groups over time for any of the functional scales, although there was trend towards better physical function scores for TAMK.

These analyses were repeated for 313 patients (255 TAMK and 58 TTIL) who had no evidence of recurrence for at least 27 months after surgery to minimize the impact of disease recurrence on HRQoL (Supplementary Table 3). For these long term survivors, physical function [and](#) global HRQoL score demonstrated trends towards more favorable scores for TAMK compared with TTIL groups over time, but were not statistically significant.

### ***Health-related quality of life symptom outcomes: single-item scales***

Patients selected for TAMK or TTIL reported similar baseline scores for all single-item scales (Table 4,  $p$ =not significant, Student’s t-test). Self-reported mean scores for the single-items reflux, speech [problems](#), odynophagia, insomnia,

swallowing problems and dry mouth did not change by more than 10 points for either TAMK or TTIL at any time after surgery, [although after 6 months the TAMK group reported scores >5 points lower for odynophagia than the TTIL group](#). Dysphagia scores did not show a significant decline until 6 months after surgery for the TTIL group and 12 months after surgery for the TAMK group, respectively. Mean constipation scores did not change after TAMK, but showed a decline of 15 points for the TTIL group, that “recovered” at 6 months after surgery. All other mean single item scales deteriorated by over 10 points in the 3 months after TAMK and TTIL (Table 4). Mean pain and nausea and vomiting “recovered” to within 10 points of baseline at 6 months for the TAMK group and 12 months for the TTIL group. Insomnia recovered after 6 months for both groups. For the TAMK group, anorexia, eating problems, and taste recovered after 12 months; fatigue and dyspnea recovered after 24 months. Cough and diarrhea scores failed to “recover” within 24 months for the TAMK group. For the TTIL group, anorexia and eating problems recovered after 6 months; taste and dyspnoea recovered after 12 months. Cough and fatigue scores failed to recover within 24 months following TTIL.

Longitudinal analyses were also undertaken comparing TAMK and TTIL using GEE with propensity score [adjustment](#). Mean symptom scores for pain were significantly higher (worse) in the TTIL group compared with TAMK at every time point for two years post-operatively ([Supplementary Fig.6, p=0.036](#)). Mean scores for odynophagia were significantly worse in the TTIL group ( $p=0.04$ ), [although changes from baseline mean scores were <5 in each group at all time points](#). In addition, mean constipation scores were significantly higher (worse) for the TTIL group, with a 15 point difference in mean score at 3 months post operatively ([Supplementary Fig 7, p=0.037](#)).

These analyses were repeated for 313 patients (255 TAMK and 58 TTIL) who had no evidence of recurrence for at least 27 months after surgery (Supplementary Table 4). For these long term survivors, mean symptom scores for pain, odynophagia, and constipation were >5 points higher (worse) in the TTIL group compared with TAMK 6 months to two years post-operatively but did not reach statistical significance.

## **DISCUSSION:**

To further supplement decision-making, this study examined the impact of TTIL and TAMK on self-reported health-related quality of life in a prospective non-randomized cohort of patients. After adjusting for known confounding factors it was observed that patients undergoing TAMK reported fewer HRQL problems, significantly less pain, constipation, in the first 24 months after surgery than patients selected for TTIL. This is an important finding and further work is needed to establish whether TAMK confers this observed patient benefit in the longer term.

Several studies have compared HRQL in MIE to open surgery but there are a lack of prospective studies with comprehensive HRQL assessments and long term follow up.<sup>2, 7, 31</sup> There is also a lack of comparative randomized and non-randomized data in this setting.<sup>4, 32</sup> Three small non-randomized comparison studies between MIE and open surgery are published.<sup>8,9,11</sup> To date, there are only two randomized studies, one assessing 114 patients (59 open esophagectomy versus 59 MIE) but the authors only followed up patients for 12 weeks post operatively,<sup>10</sup> and one assessing 64 patients (31 open versus 33 MIE) with 1 year follow up.<sup>12</sup> The studies used the EORTC generic and disease specific measures, QLQ-C30 and QLQ-OES18 to assess HRQL and they both reported a significant decline in physical function, global quality of life (QoL) and pain with faster recovery in the MIE group.<sup>10, 12</sup> In the

current study similar early reduction in physical, role, and social function was observed in both groups post operatively, but there was faster recovery in the TAMK group. These results were also observed for the subset of long term survivors who showed now evidence of disease recurrence for at least 27 months after surgery. All studies showed early differences between the groups in physical functioning recovery. Zeng et al analyzed HRQL data in open versus MIE up to 24 weeks post operatively and found a significant early decrease in social function in the open group. Wang et al reported a non-randomized comparison of 27 patients selected for thoracoscopic mobilization with 29 selected for standard open esophagectomy and found global health scores to be significantly better in the minimal access group.<sup>9</sup> Parameswaran et al reported a two centre non-randomized study of open and minimally invasive approaches to esophagectomy. It was found that all patients had decreased ability to perform activities of daily living after all types of surgical approaches but more rapid improvements were observed after MIE.<sup>11</sup> This study, however, did not adjust for baseline differences in the highly selected patients. In the largest study (which was randomized) assessing 114 patients, significant declines in physical and global quality of life (QoL) with faster recovery in the MIE group were found.<sup>10</sup> We demonstrated a slight decrease in emotional and global QoL scores post operatively but an actual improvement thereafter, with scores being higher than baseline at 2 years.

Some studies report significant functional symptoms such as reflux or dumping following esophagectomy but preserved QoL with the explanation that despite even potentially debilitating symptoms, QoL is preserved because patients are happy to be alive and disease-free.<sup>33</sup> With regard to symptom scores, most mean single item scales deteriorated by over 10 points in the 3 months after TAMK and TTIL with

pain nausea and vomiting “recovering” to within 10 points of baseline at 6 months for the TAMK group and 12 months for the TTIL group. This is consistent with previous studies consistently showing a more rapid return to baseline for MIE.<sup>8-11</sup> Other comparison studies have shown significant reflux postoperatively in both MIE and open, which we did not find, this may be related to anastomotic technique.<sup>8,9</sup> Having performed longitudinal analyses using GEE mean symptom scores for pain were significantly higher in the TTIL group compared with TAMK for two years post-operatively, although for the subset of long term survivors the observed >5 point differences did not reach statistical significance. In addition, mean constipation scores were significantly higher for the TTIL group. We feel that these outcomes are related, increased ingestion of opiate analgesia resulting in constipation. Three other comparison studies have shown an association with MIE and decreased pain scores.<sup>8-10</sup> However, they only followed patients for 24 weeks postoperatively and cannot comment on whether patients do return to baseline after this time period.

Our study is a comprehensive analysis of longitudinal HRQL (from baseline to >2 years post operatively) in a large cohort (487 patients), including subset analyses of long term survivors. The high compliance rate and the use of a validated multi-dimensional questionnaire minimizes both selection and information bias. The prospective and longitudinal design also strengthens the study. Limitations to this study include the fact [that](#) it is a non-randomized comparison study and therefore observed differences in HRQL may reflect other clinical variables that were not adjusted for. Moreover, all patients were treated by a single, high volume surgical unit potentially limiting the generalizability of the findings. There were more patients with SCC in the TAMK group, while there were more stage III patients in the TTIL group. These differences are the result of our policy of minimal gastric involvement



to allow cervical anastomosis (with SCC and smaller tumours less likely to involve >2cm of gastric cardia), rather than deliberate selection of earlier tumours for TAMK. SCC histology and stage III and IV disease have been associated with worse HRQL scores 6 months after surgery in a large population-based HRQL study from Sweden.<sup>34</sup> We adjusted for these and other factors known to be associated with HRQL (neoadjuvant treatment, age and gender) in our final analysis using propensity score [adjustment](#) as well as repeating the analyses for the subset of long term survivors and HRQL parameters remained better for the TAMK group.

For esophageal cancer, where several surgical options are available including open, hybrid MIE and total MIE, HRQL scores can help to guide therapy by allowing patients and clinicians to make more informed treatment decisions. This prospective study provides data to support the view that TAMK is a reasonable surgical choice because it has a less, albeit modest, deleterious impact on HRQL. Given that the observed differences were largely related to pain, our data suggest that thoracoscopy, rather than anastomotic site, has some HRQoL-related benefits over thoracotomy. This study highlights the need for further comparative HRQL studies with prospective, long term follow up from multiple surgical units to determine the applicability of the results in the broader context. In particular, studies of thoracoscopically-assisted esophagectomy comparing anastomotic site in the neck with the chest (Ivor Lewis) are areas for further research. Such studies would support the need for a randomized clinical trial designed to address HRQL outcomes over the short, medium and long term to confirm the benefits we have found.

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### Figure Legend

Figure 1:

Consort Diagram for study. MIE=Minimally Invasive Esophagectomy.

HRQL=Health Related Quality of Life.

Supplementary Figure 1:

Mirrored histogram of propensity scores by relative frequency for both groups.

TAMK=Thoracoscopically Assisted McKeown esophagectomy, TTIL=Transthoracic Ivor Lewis esophagectomy.

Supplementary Figure 2:

Kaplan Meier Survival Curve and Table for both groups. TAMK=Thoracoscopically Assisted McKeown esophagectomy, TTIL=Transthoracic Ivor Lewis esophagectomy.

Supplementary Figure 3

Graph of mean physical function scores over time for both groups, [adjusted for propensity scores](#). TAMK=Thoracoscopically Assisted McKeown esophagectomy, TTIL=Transthoracic Ivor Lewis esophagectomy.

Supplementary Figure 4



Graph of mean emotional function scores over time for both groups, [adjusted for propensity scores](#). TAMK=Thoracoscopically Assisted McKeown esophagectomy, TTIL=Transthoracic Ivor Lewis esophagectomy.. SE=Standard Error.

Supplementary Figure 5

Graph of mean global Quality of Life scores over time for both groups, [adjusted for propensity scores](#). TAMK=Thoracoscopically Assisted McKeown esophagectomy, TTIL=Transthoracic Ivor Lewis esophagectomy. SE=Standard Error.

Supplementary Figure 6

Graph of mean pain scores over time for both groups, [adjusted for propensity scores](#). TAMK=Thoracoscopically Assisted McKeown esophagectomy, TTIL=Transthoracic Ivor Lewis esophagectomy. SE=Standard Error.

Supplementary Figure 7

Graph of mean constipation scores over time for both groups, [adjusted for propensity scores](#). TAMK=Thoracoscopically Assisted McKeown esophagectomy, TTIL=Transthoracic Ivor Lewis esophagectomy.. SE=Standard Error.